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EXAMINER	
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Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents

See the attached.

1. Claims 47-80 are pending in the instant application.

Applicant elected the invention of Group I and chimeric opioid receptors as the species (claims 47, 48-52, 59 and 63-67).

Claims 53-58, 60-62, and 68-80 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected specie. Election was made **without** traverse in Paper No. 12.

2. Acknowledgment is made of applicant's claim for foreign priority based on application PCT/US94/05747 on May 20, 1994. It is noted, however, that applicant has not filed a certified copy of the application as required by 35 U.S.C. 119(b).

3. The Declaration of Dr. Terry Reisine, submitted September 17, 1997, is acknowledged.

4. The specification does not comply with §1.821(d) of the Sequence Rules and Regulations. When the description or claims of a patent application discuss a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of the Sequence Rules and Regulation, reference must be made to the sequence by use of the assigned identifier, in the text of the description and claims of the patent application. Further, § 2422.02 of the MPEP states, "...when a sequence is presented in a drawing,...the sequence identifier (SEQ ID NO: X) must be used

either in the drawing or in the Brief Description of Drawings." Figures 1, 3, and 4 disclose sequences that are not referenced by sequence identifiers.

5. Claims 47-51, 59, and 63-65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 47 is vague and indefinite because part (b) is unclear. It is not clear as to what is involved in testing the ability of said substance to interact with said opioid receptor. The claim should set forth all the required steps in a sequential manner. First of all, is the substance incubated with the opioid receptor ? Secondly, is the binding of the substance to the opioid receptor measured or detected?

In claims 48 and 63, the term "chimeric opioid receptor polypeptide" is vague and indefinite because it is not clear as to what polypeptides are encompassed by the term. Is the term limited to chimeric polypeptide comprising two different classes of opioid receptor or does the term encompass chimeric polypeptide comprising an opioid receptor linked to a non-opioid receptor? It is pointed out that claim 48 is dependent from claim 47, and claim 63 is dependent from claim 59. Claims 47 and 59 are directed to a method of screening a substance for binding to an opioid receptor. A chimeric polypeptide comprising an opioid receptor linked to a non-opioid receptor is not an opioid receptor. Thus, if the term "chimeric opioid receptor" encompasses an

opioid receptor linked to a non-opioid receptor, then claims 48 and 63 are improper dependent claims.

In claims 49, 50, 64 and 65, it is not clear as to what the second component of the chimeric polypeptide is. A chimeric polypeptide comprises at least two different components. Only one component is recited in the claims.

Claim 51 is vague and indefinite because a verb such as comprising or consisting seems to be missing and because "the polypeptide portions" lacks antecedent basis.

Claim 59 is confusing. First of all, the goal recited in the preamble does not seem to be consistent with the recited steps. The preamble of the claim seems to be drawn to a method of making an agonist of a kappa opioid receptor, but the recited method steps seem to be drawn to a method of screening for compounds capable of interacting with any opioid receptor. In fact, the first step is directed to providing an opioid receptor polypeptide. The method steps are not drawn to a method of making an agonist of a kappa opioid receptor. It is suggested that the preamble of the claim be amended to recite, "A method of screening for an agonist of a kappa opioid receptor. Secondly, it is not clear as to what is involved in "obtaining a candidate specific kappa opioid receptor agonist". Does it need to be shown that it is kappa opioid receptor agonist? Thirdly, "said substance" in step (c) lacks antecedent basis. Fourthly, it is not clear as to what is involved in testing the ability of "said substance" to interact with said opioid receptor. Does the step involve incubating the receptor with the candidate agonist and detecting binding between the receptor and the candidate agonist? The claim should recite the steps involved in part (c) of the

claim. Fifthly, it is not clear how part (d) flows from part (c). There is no connection between the two steps. Lastly, it is not clear as to what is encompassed by the term "specific agonist of a kappa opioid receptor." Does the substance only act as an agonist of a kappa opioid receptor? Can the substance act as an agonist or an antagonist of other opioid receptors?

6. Claims 47-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of screening a substance for binding to kappa and delta opioid receptors or chimeric opioid receptors comprising a region of the delta opioid receptor linked to a portion of the kappa opioid receptor, does not reasonably provide enablement for the diverse genus of chimeric opioid receptors encompassed by the term. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 47 is directed to a method of screening a substance for binding to an opioid receptor and claims 48-51 are limited to a method of screening a substance for binding to a chimeric opioid receptor. The term "opioid receptor polypeptide" or "chimeric opioid receptor polypeptide" broadly encompasses opioid receptors that are not disclosed by the specification. To obtain chimeric opioid receptor, it is necessary to have the nucleic acid encoding the opioid receptors because chimeric opioid receptors, as taught by the specification, are produced by fusing the nucleic acids encoding two different opioid receptors and expressing the fused nucleic acid in a host cell to produce the encoded polypeptide. The specification only discloses the

nucleic acids encoding kappa opioid receptor and delta opioid receptor, and the prior art only teaches the nucleic acid encoding delta opioid receptor. Although it is known that other opioid receptors, such as mu opioid receptor existed, the specification and prior art does not disclose the nucleic acid encoding the mu opioid receptor and does not provide sufficient guidance for obtaining the nucleic acid encoding other mu opioid receptor. It is not predictable as to where the nucleic acids encoding other opioid receptors are expressed, whether they are related to the nucleic acid encoding kappa and delta opioid receptor, and whether they can be isolated by routine cloning methods. It is also not predictable as to what nucleic acid sequences encode the other opioid receptors. As shown by the specification, each class of opioid receptor has a distinct amino acid sequence and is encoded by a distinct nucleic acid sequences. The kappa opioid receptor and the delta opioid receptor have different amino acid sequences. Although their amino acid sequences are related because they are both opioid receptors, their sequences are not identical, since they have distinct binding properties and interact with different ligands. Thus, the amino acid or nucleic acid of one opioid receptor is not predictive of the other opioid receptor. Accordingly, without the nucleic acid encoding other opioid receptors and without the guidance from the specification or the prior art for obtaining them, it would require undue experimentation of the skilled artisan to practice the claimed method using a diverse genus of chimeric opioid receptor polypeptide encompassed by the specification.

7. Claims 59 and 63-65 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a process of making a product with an ability to act as a specific agonist of a kappa opioid receptor. The claims are not enabled by the specification for the following reasons. First of all, the recited steps are directed to a method of screening for a substance that interacts with the opioid receptor. The recited steps are not directed to making any product. Secondly, the recited steps do not enable the skilled artisan to distinguish an agonist from an antagonist of kappa opioid receptor. Both the agonist and the antagonist interact with the kappa opioid receptor. However, the agonist mediates the activity of the receptor while the antagonist blocks the activity of the receptor. Thirdly, the specification does not enable the use of any opioid receptor to screen for an agonist for the kappa opioid receptor. As discussed above under the previous rejection, each opioid receptor has a unique amino acid sequence and interacts with a unique set of ligands. An agonist for a delta opioid receptor will not act as an agonist for a kappa opioid receptor. Lastly, the specification only enables the claimed method using delta and kappa opioid receptor and chimeric opioid receptors comprising portions of the delta opioid receptor and portions of the kappa opioid receptor for the reasons discussed under the previous rejection under § 112, first paragraph.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 47 is rejected under 35 U.S.C. 102(a) as being anticipated by Evans et al. or Kieffer et al.

Evans discloses a method of screening for ligands that interact with the delta opioid receptor (page 1953). The method of Evans comprises providing COS cells expressing the delta opioid receptor, incubating the COS cells with labeled ligands, and detecting the binding of the ligand to the delta opioid receptor expressed on the surface of COS cells.

Kieffer discloses a method of screening for ligands that interact with the delta opioid receptor (page 12049). The method of Kieffer comprises providing COS cells expressing the delta opioid receptor, obtaining a membrane preparation from the COS cells, incubating the membrane preparation with labeled ligands, and detecting the binding of the ligand to the delta opioid receptor expressed on the membranes of the COS cells.

Thus, the claims are anticipated by Evans or Kieffer.

10. Claims 47 and 59 are rejected under 35 U.S.C. 102(b) as being anticipated by Ahmed et al.

Claim 59 is interpreted as directed to a method of screening for agonists of kappa opioid receptor

Ahmed discloses a method of screening for ligands that interact with the human kappa opioid receptor (page 862). The method of Ahmed comprises providing purified human kappa opioid receptor, incubating the purified receptor with labeled ligands, and detecting the binding of the ligand to the kappa opioid receptor. Ahmed also performed competition assays to determine compounds that act as agonists of human kappa opioid receptor (pages 865-868). The competition assay comprises incubating purified human kappa opioid receptor with known agonists and labeled ligand and determining the IC_{50} of the binding of the receptor to the labeled ligands in the presence of known agonists. Thus, the claims are anticipated by Ahmed.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 48-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evans et al. in view of Frielle et al.

Evans discloses a method of screening for ligands that interact with the delta opioid receptor (page 1953). The method of Evans comprises providing COS cells expressing the delta opioid receptor, incubating the COS cells with various labeled ligands, and detecting the binding of the ligand to the delta opioid receptor expressed on the surface of COS cells. Evans shows in figure 3 that the delta opioid receptor is a G-protein coupled receptor and is related to the well known somatostatin receptor. However, Evans does not disclose a method of screening for ligands that interact with chimeric delta opioid receptor.

Frielle teaches the use of chimeric β1/β2 adrenergic receptors in binding assays for determining the structure/function relationship of adrenergic receptors. In figure 2, Frielle shows that the chimeric adrenergic receptors of Frielle comprise a portion of the β1-adrenergic receptor linked to an alternate portion of the β2-adrenergic receptor. The results from the binding assay using the chimeric β-adrenergic receptor suggest that the different transmembrane regions may play a role in agonist and antagonist binding.

Since Frielle provides method steps for obtaining chimeric β-adrenergic receptor, and shows that chimeric β-adrenergic receptors, which are also G-protein coupled receptors, are useful for ligand binding assays, the skilled artisan would have reasonably expected to successfully obtain chimeric delta opioid receptors wherein a portion of the delta opioid receptor is replaced by a closely receptor, such as the well known somatostatin receptor (see Evans fig. 3) and to use the chimeric delta opioid receptors in ligand binding assays for obtaining ligands that interact with the chimeric delta opioid receptor. Accordingly, it would have been obvious to the skilled artisan at the time the invention was made to modify the ligand binding assay of Evans by using chimeric delta opioid receptor obtained by replacing a portion of the delta opioid receptor such as the seventh transmembrane domain and the following carboxyl terminus with that from the somatostatin receptor, as taught by Frielle in figure 2G for the chimeric β-adrenergic receptor, with the expectation of obtaining a chimeric opioid receptor that can be used in a ligand binding assay. The motivation to use chimeric delta opioid receptors in the ligand binding assay is that chimeric delta opioid receptors have different binding properties and would enable the skilled artisan to obtain more ligands that interact with opioid receptors.

Thus, the claims are *prima facie* obvious over the prior art.

12. Claims 52, 66, and 67 are objected to for depending upon rejected claims. These claims would be allowable if rewritten in independent form.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sally Teng, Ph.D., whose telephone number is (703) 308-4230. The examiner can normally be reached on Mon.-Fri. from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Stephen Walsh, can be reached on (703) 308-2957.

Official papers filed by fax should be directed to (703) 305-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**stephen.walsh@uspto.gov**].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

October 24, 1997

Sally Teng